Complete Summary

GUIDELINE TITLE

2007 guidelines for the management of arterial hypertension.

BIBLIOGRAPHIC SOURCE(S)

Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Struijker Boudier HA, Zanchetti A, ESC Committee for Practice Guidelines (CPG):, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, ESH Scientific Council:, Kjeldsen SE, Erdine S, Narkiewicz K, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Cifkova R, Dominiczak A, Fagard R, Heagerty AM, Laurent S, Lindholm LH, Mancia G, Manolis A, Nilsson PM, Redon J, Schmieder RE, Struijker-Boudier HA, Viigimaa M, Document Reviewers:, Filippatos G, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Kiowski W, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Viigimaa M, Waeber B, Williams B, Zamorano JL. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2007 Jun;28(12):1462-536. [825 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This updates a previous guideline: 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2003 Jun;21(6):1011-53.

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
CONTRAINDICATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Hypertension

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Risk Assessment
Treatment

CLINICAL SPECIALTY

Cardiology
Family Practice
Internal Medicine

INTENDED USERS

Advanced Practice Nurses
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To offer the best available and most balanced recommendation to all health care providers involved in the management of hypertension
- To provide guidelines that have been prepared on the basis of the best available evidence on all issues deserving recommendations, and with the consideration that guidelines should have an educational purpose more than a prescriptive one

TARGET POPULATION

Patients with hypertension

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Repeated blood pressure (BP) measurements
2. Medical history
3. Physical examination for evidence of additional risk factors (in particular abdominal obesity), for signs suggesting secondary hypertension, and for evidence of organ damage
4. Laboratory and instrumental investigations

- Fasting plasma glucose
- Serum total cholesterol
- Serum low density lipoprotein (LDL)-Cholesterol
- Serum high density lipoprotein (HDL)-cholesterol
- Fasting serum triglycerides
- Serum uric acid
- Serum creatinine
- Serum potassium
- Estimated creatine clearance (Cockroft-Gault formula) or glomerular filtration rate (Modification of Diet in Renal Disease formula)
- Haemoglobin and haematocrit
- Urinalysis (complemented by microalbuminuria via dipstick test and microscopic examination)
- Electrocardiogram

5. Echocardiogram
6. Carotid ultrasound
7. Quantitative proteinuria (if dipstick positive)
8. Ankle-brachial BP index
9. Fundoscopy
10. Glucose tolerance test (if fasting plasma glucose >5.6 mmol/L (100 mg/dL)
11. Home and 24 hour ambulatory BP monitoring
12. Pulse wave velocity measurement (where available)
13. Searching for subclinical organ damage

Treatment

1. Lifestyle changes including smoking cessation, weight reduction, reduction of excessive alcohol intake, physical exercise, reduction of salt intake, and increase in fruit and vegetable intake and decrease in saturated and total fat intake
2. Calcium antagonists
3. Angiotensin-converting enzyme inhibitors
4. Thiazide diuretics
5. Beta blockers
6. Angiotensin receptor antagonist
7. Alpha-blockers
8. Monotherapy versus combination therapy
9. Treatment of associated risk factors
10. Patient follow up
11. Improvement of patient compliance
12. Management of hypertension in patient subgroups (elderly, diabetics, patients with renal dysfunction, cerebrovascular disease, coronary heart disease and heart failure, women)

MAJOR OUTCOMES CONSIDERED

- Total cardiovascular risk
- All-cause morbidity and mortality
- Left ventricular hypertrophy
- Presence of atherosclerosis

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Searches were performed of the following resources: PubMed, medical journals by speciality, the Cochrane Library.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The members of the Guidelines Committee established by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) have participated independently in the preparation of this document, drawing on their academic and clinical experience and applying an objective and critical examination of all available literature.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Cost-effectiveness of Antihypertensive Treatment

Several studies have shown that in high or very high risk patients, treatment of hypertension is largely cost effective, that is that the reduction in the incidence of cardiovascular disease and death largely offsets the cost of treatment despite its lifetime duration. Indeed, it is likely that the benefit is even greater than that calculated by the number of events saved per year of treatment and expressed by the so called number needed to treat or ,'NNT'. 1) In several placebo-controlled trials a substantial number of patients randomized to placebo received treatment and a number of patients allocated to active treatment actually withdrew from it while continuing to be considered in the original groups according to the intention-to-treat principle; 2) Some trials show that the difference in event incidence between treated and placebo groups increases progressively over the few years of the trial duration, raising the possibility of a greater long-term protective effect of blood pressure reductions; 3) In younger low risk hypertensives what appears to be as a relatively small benefit when calculated over a treatment period of 5 years may translate into a more substantial number of added life years compared with elderly high risk hypertensives. This implies that in younger subjects actuarial information may provide a better assessment of the benefit than data obtained in trials. In young patients the purpose of treatment is not to prevent an unlikely morbid or fatal event in the subsequent few years, but rather to prevent onset and/or progression of organ damage that will, in the long term, convert the low risk patient into a higher risk one. Several trials of antihypertensive therapy, foremost the HDFP and HOT studies, have shown that despite intense blood pressure lowering the incidence of cardiovascular events remains much higher in high risk hypertensives or hypertensives with complications than in hypertensives with initial low or moderate risk. This suggests that some of the major cardiovascular risk changes may be difficult to reverse, and that restricting antihypertensive therapy to patients at high or very high risk may be far from an optimal strategy. Finally, the cost of drug treatment of hypertension is often contrasted to lifestyle measures, which are considered cost-free. However, real implementation, and therefore effectiveness, of lifestyle changes requires behavioural support, counselling and reinforcement, the cost of which may not be negligible.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Once the document was finalized and approved by all the experts involved in the Task Force, it was submitted to outside specialists for review. In some cases, the document would be presented to a panel of key opinion leaders in Europe, specialists in the relevant condition at hand, for discussion and critical review. If necessary, the document was revised once more and, finally, approved by both the European Society of Hypertension and the European Society of Cardiology (ESC) Committee for Practice Guidelines (CPG) and selected members of the board of the ESC.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The following is a brief statement of the practice recommendations for the management of hypertension. The reader should refer to the original guideline document for detailed management recommendations and a critical assessment of the evidence for the recommendations.

Table 1: Definitions and Classifications of Blood Pressure Levels (mmHg)

Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

Isolated systolic hypertension should be graded (1, 2, 3) according to systolic blood pressure values in the ranges indicated, provided that diastolic values are <90 mmHg. Grades 1, 2 and 3 correspond to a classification in mild, moderate and severe hypertension, respectively. These terms have now been omitted to avoid confusion with quantification of total cardiovascular risk.

Total cardiovascular (CV) risk

- Dysmetabolic risk factors and subclinical organ damage are common in hypertensive patients.
- All patients should be classified not only in relation to the grades of hypertension but also in terms of the total cardiovascular risk resulting from the coexistence of different risk factors, organ damage and disease.
- Decisions on treatment strategies (initiation of drug treatment, Blood Pressure (BP) threshold and target for treatment, use of combination treatment, need of a statin and other non-antihypertensive drugs) all importantly depend on the initial level of risk.
- There are several methods by which total cardiovascular risk can be assessed, all with advantages and limitations. Categorization of total risk as low, moderate, high, and very high added risk has the merit of simplicity and can therefore be recommended. The term 'added risk' refers to the risk additional to the average one. (See Figure 1 in the original guideline document: Stratification of CV Risk)

- Total risk is usually expressed as the absolute risk of having a cardiovascular event within 10 years. Because of its heavy dependence on age, in young patients absolute total cardiovascular risk can be low even in the presence of high BP with additional risk factors. If insufficiently treated, however, this condition may lead to a partly irreversible high risk condition years later. In younger subjects treatment decisions should better be guided by quantification of relative risk (i.e. the increase in risk in relation to average risk in the population).

Blood pressure (BP) measurement

When measuring BP, care should be taken to:

- Allow the patients to sit for several minutes in a quiet room before beginning BP measurements.
- Take at least two measurements spaced by 1–2 minutes, and additional measurements if the first two are quite different.
- Use a standard bladder (12–13 cm long and 35 cm wide) but have a larger and a smaller bladder available for fat and thin arms, respectively. Use the smaller bladder in children.
- Have the cuff at the heart level, whatever the position of the patient.
- Use phase I and V (disappearance) Korotkoff sounds to identify systolic and diastolic BP, respectively.
- Measure BP in both arms at first visit to detect possible differences due to peripheral vascular disease. In this instance, take the higher value as the reference one.
- Measure BP 1 and 5 minutes after assumption of the standing position in elderly subjects, diabetic patients, and in other conditions in which postural hypotension may be frequent or suspected.
- Measure heart rate by pulse palpation (at least 30 sec) after the second measurement in the sitting position.

Ambulatory and home BP measurement

Ambulatory BP

- Although office BP should be used as reference, ambulatory BP may improve prediction of cardiovascular risk in untreated and treated patients.
- Normal values are different for office and ambulatory BP. (See Table 2 below.)
- Twenty-four-hour ambulatory BP monitoring should be considered in particular, when
    - Considerable variability of office BP is found over the same or different visits.
    - High office BP is measured in subjects otherwise at low total cardiovascular risk.
    - There is marked discrepancy between BP values measured in the office and at home.
    - Resistance to drug treatment is suspected.
    - Hypotensive episodes are suspected, particularly in elderly and diabetic patients

- Office BP is elevated in pregnant women and pre-eclampsia is suspected

Home BP

- Self-measurement of BP at home is of clinical value and its prognostic significance is now demonstrated. These measurements should be encouraged in order to:
  - Provide more information on the BP lowering effect of treatment at trough, and thus on therapeutic coverage throughout the dose-to-dose time interval
  - Improve patient's adherence to treatment regimens
  - There are doubts on technical reliability/environmental conditions of ambulatory BP data
- Self-measurement of BP at home should be discouraged whenever:
  - It causes anxiety to the patient.
  - It induces self-modification of the treatment regimen.
- Normal values are different for office, ambulatory, and home BP (See Table 2 below)

Table 2: Blood Pressure Thresholds (mmHg) for Definition of Hypertension with Different Types of Measurement

	Systolic Blood Pressure (SBP)	Diastolic Blood Pressure (DBP)
Office or Clinic	140	90
24-hour	125–130	80
Day	130–135	85
Night	120	70
Home	130–135	85

Guidelines for family and clinical history

- Duration and previous level of high BP
- Indications of secondary hypertension
  - Family history of renal disease (polycystic kidney)
  - Renal disease, urinary tract infection, haematuria, analgesic abuse (parenchymal renal disease)
  - Drug/substance intake: oral contraceptives, liquorice, carbenoxolone, nasal drops, cocaine, amphetamines, steroids, non-steroidal anti-inflammatory drugs, erythropoietin, cyclosporin
  - Episodes of sweating, headache, anxiety, palpitation (phaeochromocytoma)
  - Episodes of muscle weakness and tetany (aldosteronism).
- Risk factors
  - Family and personal history of hypertension and cardiovascular disease
  - Family and personal history of dyslipidaemia
  - Family and personal history of diabetes mellitus
  - Smoking habits
  - Dietary habits
  - Obesity; amount of physical exercise
  - Snoring; sleep apnea (information also from partner)

    - Personality
- Symptoms of organ damage
    - Brain and eyes: headache, vertigo, impaired vision, transient ischaemic attacks, sensory or motor deficit
    - Heart: palpitation, chest pain, shortness of breath, swollen ankles
    - Kidney: thirst, polyuria, nocturia, haematuria
    - Peripheral arteries: cold extremities, intermittent claudication
- Previous antihypertensive therapy
    - Drug(s) used, efficacy and adverse effects
- Personal, family, and environmental factors

Physical examination for secondary hypertension, organ damage and visceral obesity

Signs suggesting secondary hypertension and organ damage

- Features of Cushing syndrome
- Skin stigmata of neurofibromatosis (phaeochromocytoma)
- Palpation of enlarged kidneys (polycystic kidney)
- Auscultation of abdominal murmurs (renovascular hypertension)
- Auscultation of precordial or chest murmurs (aortic coarctation or aortic disease)
- Diminished and delayed femoral and reduced femoral BP (aortic coarctation, aortic disease)

Signs of organ damage

- Brain: murmurs over neck arteries, motor or sensory defects
- Retina: funduscopic abnormalities
- Heart: location and characteristics of apical impulse, abnormal cardiac rhythms, ventricular gallop, pulmonary rales, peripheral oedema
- Peripheral arteries: absence, reduction, or asymmetry of pulses, cold extremities, ischaemic skin lesions
- Carotid Arteries: systolic murmurs

Evidence of visceral obesity

- Body weight
- Increased waist circumference (standing position) M: > 102 cm; F: > 88 cm
- Increased body mass index [body weight (kg)/height $(m)^2$]
- Overweight $\geq$25 kg/m^2; Obesity $\geq$30 kg/m2

Laboratory investigations

Routine tests

- Fasting plasma glucose
- Serum total cholesterol
- Serum LDL-Cholesterol
- Serum HDL-cholesterol
- Fasting serum triglycerides

- Serum potassium
- Serum uric acid
- Serum creatinine
- Estimated creatine clearance (Cockroft-Gault formula) or glomerular filtration rate (Modification of Diet in Renal Disease formula)
- Haemoglobin and haematocrit
- Urinalysis (complemented by microalbuminuria via dipstick test and microscopic examination)
- Electrocardiogram

Recommended tests

- Echocardiogram
- Carotid ultrasound
- Quantitative proteinuria (if dipstick test positive)
- Ankle-brachial BP index
- Fundoscopy
- Glucose tolerance test (if fasting plasma glucose >5.6 mmol/L (100 mg/dL)
- Home and 24 hours ambulatory BP monitoring
- Pulse wave velocity measurement (where available)

Extended evaluation (domain of the specialist)

- Further search for cerebral, cardiac, renal and vascular damage. Mandatory in complicated hypertension
- Search for secondary hypertension when suggested by history, physical examination or routine tests: measurement of renin, aldosterone, corticosteroids, catecholamines in plasma and/or urine; arteriographies; renal and adrenal ultrasound; computer-assisted tomography; magnetic resonance imaging

Searching for subclinical organ damage

Due to the importance of subclinical organ damage as an intermediate stage in the continuum of vascular disease and as a determinant of total cardiovascular risk, signs of organ involvement should be sought carefully by appropriate techniques:

- Heart – Electrocardiography should be part of all routine assessment of subjects with high BP in order to detect left ventricular hypertrophy, patterns of "strain," ischaemia and arrhythmias. Echocardiography is recommended when a more sensitive detection of left ventricular hypertrophy is considered useful. Geometric patterns can be defined echocardiographically, of which concentric hypertrophy carries the worse prognosis. Diastolic dysfunction can be evaluated by transmitral Doppler.
- Blood vessels – Ultrasound scanning of carotid arteries is recommended when detection of vascular hypertrophy or asymptomatic atherosclerosis is deemed useful. Large artery stiffening (leading to isolated systolic hypertension in the elderly) can be measured by pulse wave velocity. It might be more widely recommended if its availability were greater. A low ankle-brachial BP index signals advanced peripheral artery disease.

- Kidney – Diagnosis of hypertension-related renal damage is based on a reduced renal function or an elevated urinary excretion of albumin. Estimation from serum creatinine of glomerular filtration rate (MDRD formula, requiring age, gender, race) or creatinine clearance (Cockroft–Gault formula, requiring also body weight) should be routine procedure. Urinary protein should be sought in all hypertensives by dipstick. In dipstick negative patients low grade albuminuria (microalbuminuria) should be determined in spot urine and related to urinary creatinine excretion.
- Fundoscopy – Examination of eye grounds is recommended in severe hypertensives only. Mild retinal changes are largely non-specific except in young patients. Haemorrhages, exudates and papilloedema, only present in severe hypertension, are associated with increased CV risk.
- Brain – Silent brain infarcts, lacunar infarctions, microbleeds and white matter lesions are not infrequent in hypertensives, and can be detected by magnetic resonance imaging (MRI), or computed tomography (CT). Availability and costs do not allow indiscriminate use of these techniques. In elderly hypertensives, cognitive tests may help to detect initial brain deterioration. (See Table 4 in the original guideline document for a summary of the availability, prognostic value and cost of procedures to detect subclinical organ damage.)

Goals of treatment

- In hypertensive patients, the primary goal of treatment is to achieve maximum reduction in the long-term total risk of cardiovascular disease.
- This requires treatment of the raised BP *per se* as well as of all associated reversible risk factors.
- BP should be reduced to at least below 140/90mmHg (systolic/diastolic), and to lower values, if tolerated, in all hypertensive patients.
- Target BP should be at least <130/80mmHg in diabetics and in high or very high risk patients, such as those with associated clinical conditions (stroke, myocardial infarction, renal dysfunction, proteinuria).
- Despite use of combination treatment, reducing systolic BP to <140mmHg may be difficult and more so if the target is a reduction to <130mmHg. Additional difficulties should be expected in elderly and diabetic patients, and, in general, in patients with cardiovascular damage.
- In order to more easily achieve goal BP, antihypertensive treatment should be initiated before significant cardiovascular damage develops.

Lifestyle changes

- Lifestyle measures should be instituted, whenever appropriate, in all patients, including those who require drug treatment. The purpose is to lower BP, to control other risk factors and to reduce the number of doses of antihypertensive drugs to be subsequently administered.
- Lifestyle measures are also advisable in subjects with high normal BP and additional risk factors to reduce the risk of developing hypertension.
- The lifestyle measures that are widely recognized to lower BP or cardiovascular risk, and that should be considered are:
    - Smoking cessation
    - Weight reduction (and weight stabilization)
    - Reduction of excessive alcohol intake

    - Physical exercise
    - Reduction of salt intake
    - Increase in fruit and vegetable intake and decrease in saturated and total fat intake
- Lifestyle recommendations should not be given as lip service but instituted with adequate behavioural and expert support, and reinforced periodically.
- Because long-term compliance with lifestyle measures is low and the BP response highly variable, patients under non-pharmacological treatment should be followed-up closely to start drug treatment when needed and in a timely fashion.

Choice of antihypertensive drugs

- The main benefits of antihypertensive therapy are due to lowering of BP *per se*.
- Five major classes of antihypertensive agents – thiazide diuretics, calcium antagonists, angiotensin converting enzymes (ACE) inhibitors, angiotensin receptor antagonists and beta-blockers – are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination. beta-blockers, especially in combination with a thiazide diuretic, should not be used in patients with the metabolic syndrome or at high risk of incident diabetes.
- Because in many patients more than one drug is needed, emphasis on identification of the first class of drugs to be used is often futile. Nevertheless, there are many conditions for which there is evidence in favour of some drugs versus others either as initial treatment or as part of a combination.
- The choice of a specific drug or a drug combination, and the avoidance of others, should take into account the following:
    - The previous favourable or unfavourable experience of the individual patient with a given class of compounds
    - The effect of drugs on cardiovascular risk factors in relation to the cardiovascular risk profile of the individual patient
    - The presence of subclinical organ damage, clinical cardiovascular disease, renal disease or diabetes which may be more favourably treated by some drugs than others (See recommendations on preferred drugs below and Table 6 in the original guideline document)
    - The presence of other disorders that may limit the use of particular classes of antihypertensive drugs (See Table 7 in the original guideline document)
    - The possibilities of interactions with drugs used for other conditions
    - The cost of drugs, either to the individual patient or to the health provider, but cost considerations should never predominate over efficacy, tolerability, and protection of the individual patient
- Continuing attention should be given to side effects of drugs, because they are the most important cause of non-compliance. Drugs are not equal in terms of adverse effects, particularly in individual patients.
- The BP lowering effect should last 24 hours. This can be checked by office or home BP measurements at trough or by ambulatory BP monitoring.
- Drugs which exert their antihypertensive effect over 24 hours with a once-a-day administration should be preferred because a simple treatment schedule favours compliance.

Antihypertensive Treatment: Preferred Drugs

Subclinical Organ Samage	
LVH	ACEI, CA, ARB
Asymptomatic atherosclerosis	CA, ACEI
Microalbuminuria	ACEI, ARB
Renal dysfunction	ACEI, ARB
Clinical Event	
Previous stroke	Any BP lowering agent
Previous MI	BB, ACEI, ARB
Angina pectoris	BB, CA
Heart failure	Diuretics, BB, ACEI, ARB, antialdosterone agents
Atrial fibrillation	
Recurrent	ARB, ACEI
Permanent	BB, non-dihydropyridine CA
ESRD/proteinuria	ACEI, ARB, loop diuretics
Peripheral artery disease	CA
Condition	
ISH (elderly)	Diuretics, CA
Metabolic syndrome	ACEI, ARB, CA
Diabetes mellitus	ACEI, ARB
Pregnancy	CA, methyldopa, BB
Blacks	Diuretics, CA

Abbreviations: LVH: left ventricular hypertroph; ISH: isolated systolic hypertension; ESRD: renal failure; ACEI: ACE inhibitors; ARB: angiotensin recepter antagonists; CA: calcium antagonists; BB: beta-blockers

Monotherapy versus combination therapy

- Regardless of the drug employed, monotherapy allows to achieve BP target in only a limited number of hypertensive patients.
- Use of more than one agent is necessary to achieve target BP in the majority of patients. A vast array of effective and well tolerated combinations is available.
- Initial treatment can make use of monotherapy or combination of two drugs at low doses with a subsequent increase in drug doses or number, if needed (See Figures 3 and 4 in the original guideline document).
- Monotherapy could be the initial treatment for a mild BP elevation with a low or moderate total cardiovascular risk. A combination of two drugs at low doses should be preferred as first step treatment when initial BP is in the grade 2 or 3 range or total cardiovascular risk is high or very high (Figure 3).
- Fixed combinations of two drugs can simplify treatment schedule and favour compliance.
- In several patients BP control is not achieved by two drugs, and a combination of three of more drugs is required.
- In uncomplicated hypertensives and in the elderly, antihypertensive therapy should normally be initiated gradually. In higher risk hypertensives, goal BP should be achieved more promptly, which favours initial combination therapy and quicker adjustment of doses.

Antihypertensive treatment in the elderly

- Randomized trials in patients with systolic-diastolic or isolated systolic hypertension aged ≥60 years have shown that a marked reduction in cardiovascular morbidity and mortality can be achieved with antihypertensive treatment.
- Drug treatment can be initiated with thiazide diuretics, calcium antagonists, angiotensin receptor antagonists, ACE inhibitors, and beta-blockers, in line with general guidelines. Trials specifically addressing treatment of isolated systolic hypertension have shown the benefit of thiazides and calcium antagonists but subanalysis of other trials also show efficacy of angiotensin receptor antagonists.
- Initial doses and subsequent dose titration should be more gradual because of a greater chance of undesirable effects, especially in very old and frail subjects.
- BP goal is the same as in younger patients (i.e. <140/90mmHg or below if tolerated). Many elderly patients need two or more drugs to control BP and reductions to <140mmHg systolic may be particularly difficult to obtain.
- Drug treatment should be tailored to the risk factors, target organ damage and associated cardiovascular and non-cardiovascular conditions that are frequent in the elderly. Because of the increased risk of postural hypotension, BP should always be measured also in the erect posture.
- In subjects aged 80 years and over, evidence for benefits of antihypertensive treatment is as yet inconclusive. However, there is no reason for interrupting a successful and well tolerated therapy when a patient reaches 80 years of age.

Antihypertensive treatment in diabetics

- Where applicable, intense non-pharmacological measures should be encouraged in all diabetic patients, with particular attention to weight loss and reduction of salt intake in type 2 diabetes.
- Goal BP should be <130/80mmHg and antihypertensive drug treatment may be started already when BP is in the high normal range.
- To lower BP, all effective and well tolerated drugs can be used. A combination of two or more drugs is frequently needed.
- Available evidence indicates that lowering BP also exerts a protective effect on appearance and progression of renal damage. Some additional protection can be obtained by the use of a blocker of the renin-angiotensin system (either an angiotensin receptor antagonist or an ACE inhibitor).
- A blocker of the renin-angiotensin system should be a regular component of combination treatment and the one preferred when monotherapy is sufficient.
- Microalbuminuria should prompt the use of antihypertensive drug treatment also when initial BP is in the high normal range. Blockers of the renin-angiotensin system have a pronounced antiproteinuric effect and their use should be preferred.
- Treatment strategies should consider an intervention against all cardiovascular risk factors, including a statin.
- Because of the greater chance of postural hypotension, BP should also be measured in the erect posture.

Antihypertensive therapy in patients with renal dysfunction

- Renal dysfunction and failure are associated with a very high risk of cardiovascular events.
- Protection against progression of renal dysfunction has two main requirements:
    - Strict BP control (<130/80mmHg and even lower if proteinuria is >1 g/day)
    - Lowering proteinuria to values as near to normal as possible
- To achieve the BP goal, combination therapy of several antihypertensive agents (including loop diuretics) is usually required.
- To reduce proteinuria, an angiotensin receptor blocker, an ACE inhibitor or a combination of both are required.
- There is controversial evidence as to whether blockade of the renin–angiotensin system has a specific beneficial role in preventing or retarding nephrosclerosis in non-diabetic non-proteinuric hypertensives, except perhaps in Afro-American individuals. However, inclusion of one of these agents in the combination therapy required by these patients appears well founded.
- An integrated therapeutic intervention (antihypertensive, statin and antiplatelet therapy) has to be frequently considered in patients with renal damage because, under these circumstances, cardiovascular risk is extremely high.

Antihypertensive treatment in patients with cerebrovascular disease

- In patients with a history of stroke or transient ischemic attacks, antihypertensive treatment markedly reduces the incidence of stroke recurrence and also lowers the associated high risk of cardiac events.
- Antihypertensive treatment is beneficial in hypertensive patients as well as in subjects with BP in the high normal range. BP goal should be <130/80 mmHg.
- Because evidence from trials suggests that the benefit largely depends on BP lowering *per se*, all available drugs and rational combinations can be used. Trial data have been mostly obtained with ACE inhibitors and angiotensin receptor antagonists, in association with or on the top of diuretic and conventional treatment, but more evidence is needed before their specific cerebrovascular protective properties are established.
- There is at present no evidence that BP lowering has a beneficial effect in acute stroke but more research is under way. Until more evidence is obtained antihypertensive treatment should start when post-stroke clinical conditions are stable, usually several days after the event. Additional research in this area is necessary because cognitive dysfunction is present in about 15% and dementia in 5% of subjects aged $\geq$ 65 years.
- In observational studies, cognitive decline and incidence of dementia have a positive relationship with BP values. There is some evidence that both can be somewhat delayed by antihypertensive treatment.

Antihypertensive treatment in patients with coronary heart disease and heart failure

- In patients surviving a myocardial infarction, early administration of beta-blockers, ACE inhibitors or angiotensin receptor antagonists reduces the incidence of recurrent myocardial infarction and death. These beneficial

effects can be ascribed to the specific protective properties of these drugs but possibly also to the associated small BP reduction.

- Antihypertensive treatment is also beneficial in hypertensive patients with chronic coronary heart disease. The benefit can be obtained with different drugs and drug combinations (including calcium antagonists) and appears to be related to the degree of BP reduction. A beneficial effect has been demonstrated also when initial BP is <140/90 mmHg and for achieved BP around 130/80 mmHg or less.
- A history of hypertension is common while a raised BP is relatively rare in patients with congestive heart failure. In these patients, treatment can make use of thiazide and loop diuretics, as well as of beta-blockers, ACE inhibitors, angiotensin receptor antagonists and antialdosterone drugs on top of diuretics. Calcium antagonists should be avoided unless needed to control BP or anginal symptoms.
- Diastolic heart failure is common in patients with a history of hypertension and has an adverse prognosis. There is at present no evidence on the superiority of specific antihypertensive drugs.

Hypertension in women

Treatment of hypertension in women

Response to antihypertensive agents and beneficial effects of BP lowering appear to be similar in women and in men. However, ACE inhibitors and angiotensin receptor antagonists should be avoided in pregnant and pregnancy planning women because of potential teratogenic effects during pregnancy.

Oral contraceptives

Even low oestrogen oral contraceptives are associated with increased risk of hypertension, stroke and myocardial infarction. The progestogen-only pill is a contraceptive option for women with high BP, but influence on cardiovascular outcomes has been insufficiently investigated.

Hormone replacement therapy

There is evidence that the only benefit of this therapy is a decreased incidence of bone fractures and colon cancer, accompanied, however, by increased risk of coronary events, stroke, thromboembolism, breast cancer, gallbladder disease, and dementia. This therapy is not recommended for cardioprotection in postmenopausal women.

Hypertension in pregnancy

- Hypertensive disorders in pregnancy, particularly pre-eclampsia, may adversely affect neonatal and maternal outcomes.
- Non-pharmacological management (including close supervision and restriction of activities) should be considered for pregnant women with Systolic BP (SBP) 140 to 149 mmHg or Diastolic BP (DBP) 90 to 95 mmHg. In the presence of gestational hypertension (with or without proteinuria) drug treatment is

indicated at BP levels ≥140/90 mmHg. SBP levels ≥170 or DBP ≥ 110 mmHg should be considered an emergency requiring hospitalization.
- In non-severe hypertension, oral methyldopa, labetalol, calcium antagonists and (less frequently) beta-blockers are drugs of choice.
- In pre-eclampsia with pulmonary oedema, nitroglycerine is the drug of choice. Diuretic therapy is inappropriate because plasma volume is reduced.
- As emergency, intravenous labetalol, oral methyldopa and oral nifedipine are indicated. Intravenous hydralazine is no longer the drug of choice because of an excess of perinatal adverse effects. Intravenous infusion of sodium nitroprusside is useful in hypertensive crises, but prolonged administration should be avoided.
- Calcium supplementation, fish oil and low dose aspirin are not recommended. However, low dose aspirin may be used prophylactically in women with a history of early onset pre-eclampsia.

The metabolic syndrome

- The metabolic syndrome is characterized by the variable combination of visceral obesity and alterations in glucose metabolism, lipid metabolism and BP. It has a high prevalence in the middle age and elderly population.
- Subjects with the metabolic syndrome also have a higher prevalence of microalbuminuria, left ventricular hypertrophy and arterial stiffness than those without the metabolic syndrome. Their cardiovascular risk is high and the chance of developing diabetes markedly increased.
- In patients with a metabolic syndrome diagnostic procedures should include a more in-depth assessment of subclinical organ damage. Measuring ambulatory and home BP is also desirable.
- In all individuals with metabolic syndrome, intense lifestyle measures should be adopted. When there is hypertension drug treatment should start with a drug unlikely to facilitate onset to diabetes. Therefore a blocker of the renin-angiotensin system should be used followed, if needed, by the addition of a calcium antagonist or a low-dose thiazide diuretic. It appears desirable to bring BP to the normal range.
- Lack of evidence from specific clinical trials prevents firm recommendations on use of antihypertensive drugs in all metabolic syndrome subjects with a high normal BP. There is some evidence that blocking the renin-angiotensin system may also delay incident hypertension.
- Statins and antidiabetic drugs should be given in the presence of dyslipidemia and diabetes, respectively. Insulin sensitizers have been shown to markedly reduce new onset diabetes, but their advantages and disadvantages in the presence of impaired fasting glucose or glucose intolerance as a metabolic syndrome component remain to be demonstrated

Causes of resistant hypertension

- Poor adherence to therapeutic plan
- Failure to modify lifestyle including:
    - Weight gain
    - Heavy alcohol intake (NB: binge drinking)
- Continued intake of drugs that raise BP (liquorice, cocaine, glucocorticoids, non-steroid anti-inflammatory drugs, etc.)
- Obstructive sleep apnoea

- Unsuspected secondary cause
- Irreversible or scarcely reversible organ damage
- Volume overload due to:
    - Inadequate diuretic therapy
    - Progressive renal insufficiency
    - High sodium intake
    - Hyperaldosteronism

Causes of spurious resistant hypertension

- Isolated office (white-coat) hypertension
- Failure to use large cuff on large arm
- Pseudohypertension

Treatment of associated risk factors

Lipid-lowering agents

- All hypertensive patients with established cardiovascular disease or with type 2 diabetes should be considered for statin therapy aiming at serum total and LDL cholesterol levels of, respectively, < 4.5 mmol/l (175 mg/dl) and < 2.5 mmol/l (100 mg/dl), and lower, if possible.
- Hypertensive patients without overt cardiovascular disease but with high cardiovascular risk ($\geq$20% risk of events in 10 years) should also be considered for statin treatment even if their baseline total and LDL serum cholesterol levels are not elevated.

Antiplatelet therapy

- Antiplatelet therapy, in particular low-dose aspirin, should be prescribed to hypertensive patients with previous cardiovascular events, provided that there is no excessive risk of bleeding.
- Low-dose aspirin should also be considered in hypertensive patients without a history of cardiovascular disease if older than 50 years, with a moderate increase in serum creatinine or with a high cardiovascular risk. In all these conditions, the benefit-to-risk ratio of this intervention (reduction in myocardial infarction greater than the risk of bleeding) has been proven favourable.
- To minimize the risk of haemorrhagic stroke, antiplatelet treatment should be started after achievement of BP control.

Glycaemic control

- Effective glycaemic control is of great importance in patients with hypertension and diabetes.
- In these patients dietary and drug treatment of diabetes should aim at lowering plasma fasting glucose to values $\leq$ 6 mmol/l (108 mg/dl) and at a glycated haemoglobin of <6.5%.

Patients' follow-up

- Titration to BP control requires frequent visits in order to modify the treatment regimen in relation to BP changes and appearance of side effects.
- Once target BP has been obtained, the frequency of visits can be considerably reduced. However, excessively wide intervals between visits are not advisable because they interfere with a good doctor-patient relationship, which is crucial for patient's compliance.
- Patients at low risk or with grade 1 hypertension may be seen every 6 months and regular home BP measurements may further extend this interval. Visits should be more frequent in high or very high risk patients. This is the case also in patients under non-pharmacological treatment alone due to the variable antihypertensive response and the low compliance with this intervention.
- Follow-up visits should aim at maintaining control of all reversible risk factors as well as at checking the status of organ damage. Because treatment induced changes in left ventricular mass and carotid artery wall thickness are slow, there is no reason to perform these examinations at less than 1 year intervals.
- Treatment of hypertension should be continued for life because in correctly diagnosed patient's cessation of treatment is usually followed by return to the hypertensive state. Cautious downward titration of the existing treatment may be attempted in low risk patients after long-term BP control, particularly if non-pharmacological treatment can be successfully implemented.

How to improve compliance with treatment

- Inform the patient on the risk of hypertension and the benefit of effective treatment.
- Provide clear written and oral instructions about treatment.
- Tailor the treatment regimen to patient's lifestyle and needs.
- Simplify treatment by reducing, if possible, the number of daily medicaments.
- Involve patient's partner or family in information on disease and treatment plans.
- Make use of self measurement of BP at home and of behavioural strategies such as reminder systems.
- Pay great attention to side effects (even if subtle) and be prepared to change drug doses or types if needed.
- Dialogue with patient regarding adherence and be informed of his/her problems.
- Provide reliable support system and affordable prices

CLINICAL ALGORITHM(S)

An algorithm is provided in the original guideline document for the possible combination between some classes of hypertensive therapy.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Data was primarily considered from large randomized trials and meta-analyses, but also made use where necessary of observational studies and other sources of data, provided they were obtained in studies meeting a high scientific standard.

These recommendations have been accompanied by relevant references, and those articles based on large randomized trials, meta-analyses, or large observational studies have been clearly identified in the original guideline document.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate management of patients with hypertension

POTENTIAL HARMS

Adverse events during anti-hypertensive treatment are not entirely avoidable because they may have, in part, a psychological nature and indeed are also reported during administration of placebo. Great effort should be devoted, however, to limitation of drug-related side effects and preservation of the quality of life either by switching treatment from the responsible drug to another agent or by avoiding unnecessary increases of the dose of the drug employed. Side effects of thiazide diuretics, beta-blockers and calcium antagonists are dose related whereas there is little or no dose-dependent increase in side effects with angiotensin receptor antagonists and angiotensin-converting enzyme inhibitors (ACE) inhibitors.

CONTRAINDICATIONS

CONTRAINDICATIONS

Table Compelling and Possible Contraindications to use of Antihypertensive Drugs

	Compelling	Possible
Thiazide diuretics	Gout	• Metabolic syndrome • Glucose intolerance • Pregnancy
Beta-blockers	• Asthma • Atrioventricular (A-V) block (grade 2 or 3)	• Peripheral artery disease • Metabolic syndrome • Glucose intolerance • Athletes and physically active patients • Chronic obstructive pulmonary disease
Calcium antagonists		• Tachyarrhythmias

	Compelling	Possible
(dihydropyridines)		• Heart failure
Calcium antagonists (verapamil, diltiazem)	• A-V block (grade 2 or 3) • Heart failure	
Angiotensin-converting enzyme (ACE) inhibitors	• Pregnancy • Angioneurotic oedema • Hyperkalaemia • Bilateral renal artery stenosis	
Angiotensin receptor antagonists	• Pregnancy • Hyperkalaemia • Bilateral renal artery stenosis	
Diuretics (antialdosterone)	• Renal failure • Hyperkalaemia	

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The Committee avoided a rigid classification of recommendations, by the level or strength of scientific evidence. The Committee felt this is often difficult to apply and that that it can only apply to therapeutic aspects and that strength of a recommendation can be judged from the way it is formulated and from reference to relevant studies.
- Guidelines deal with medical conditions in general and therefore their role must be educational, not prescriptive or coercive for the management of individual patients who may differ widely in their personal, medical and cultural characteristics, thus requiring decisions different from average one recommended by guidelines.
- The European Society of Cardiology (ESC) Guidelines represent the views of the ESC and were arrived at after careful consideration of the available evidence at the time they were written. Health professionals are encouraged to take them fully into account when exercising their clinical judgment. The guidelines do not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patients, in consultation with that patient, and where appropriate and necessary the patient's guardian or carer. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Despite overwhelming evidence that hypertension is a major cardiovascular risk factor and that blood pressure lowering strategies substantially reduce the risk, studies performed on various continents, as well as in several European countries, consistently show that 1) a noticeable proportion of hypertensive individuals are unaware of their condition or, if aware, do not undergo treatment, and 2) goal blood pressure levels are seldom achieved, regardless of whether treatment is prescribed and patients are followed by specialists or practitioners. Systolic blood pressure control is particularly rare, and the lower values (<130 mmHg) recommended in diabetics and very high risk patients almost exceptionally reached. This explains why high blood pressure remains a leading cause of death and cardiovascular morbidity both worldwide and in industrialized countries. It also emphasizes the strong need to extend to a larger fraction of the population the procedures that allow hypertension to be detected, as well as to 'capture' for effective treatment a substantially greater number of patients.

The purpose of the present guidelines is to help achieve this goal. However, producing guidelines alone is insufficient to address the above problem. There must be a continuous process of implementation involving education and audit. The successful implementation of guidelines requires a concerted effort of medical professionals to realize its full potential. With regard to hypertension the approach may differ between European countries. In some countries prevention of cardiovascular disease, including detection and control of hypertension, is carried out in the primary care setting under the responsibility of general practitioners as well as dedicated nurses and other health professionals. In other countries specialists and hospital physicians may be more extensively involved. Therefore guidelines issued by an international expert committee should be adapted at the national level, depending on local cultural background, socioeconomic situations, and health care organization.

A broad acceptance of the present guidelines by national hypertension societies and leagues is a prerequisite to promote management implementation in practice and improve patient outcomes. In this context, the present guidelines have been prepared in close cooperation with the Fourth Joint Task Force of European and other Societies of Cardiovascular Disease Prevention. Their recommendations are thus consistent with the recommendations that will appear in the Fourth Joint Task Force Guidelines which will also be published in 2007. Also important is that the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) are both part of a platform for Societies interested in the implementation of prevention of cardiovascular disease in clinical practice in the Joint Prevention Committee. The other partners in that platform are: the European Atherosclerosis Society, the European Association for the Study of Diabetes, the International Diabetes Federation-Europe, WONCA-Europe (European Society of General Practice/Family Medicine), the European Heart Network and the International Society of Behavioural Medicine. This partnership is crucial because general practitioners are more likely to accept and to use guidelines when these are developed with the involvement of those known to them.

Successful implementation of guidelines requires awareness of the barriers interposed between recommendations and practice. The first barrier is knowledge and acceptance by physicians. Knowledge is hampered by the high number of guidelines doctors receive, by their duplication by too many scientific societies,

local organizations, health providing agencies. Confusion is raised by even small differences in the recommendations, and the suspicion is cultivated that some guidelines may be excessively influenced by the scientific biases of the experts, or by extrinsic influences such as those of the pharmaceutical industry or of private or public health providers. Furthermore, doctors are correctly aware that their task is to manage individuals, so often different from each other, while guidelines, by necessity, are dealing with a medical condition in general. This aspect was carefully considered when the 2003 ESH-ESC Guidelines were prepared, and the choice of making them widely informative and minimally prescriptive has likely been an important reason for their acceptance. This choice has been reiterated when preparing the current guidelines.

Barriers to implementation relate not only to the clinician but also to the patient. Adherence to lifestyle changes and longterm compliance with multiple drugs are major problems. Lifestyle changes have too often been conceived as an object of preaching rather than an approach to be implemented, and as a cheap alternative to the costs of drug therapy, while a costly professional approach guided by experts in behavioural medicine is often needed.

Besides the doctor and the patient, the health care system by itself may be a barrier. Indeed, health providers sometimes wrongly consider the management of hypertension as the matter of few minute visits, and reimburse doctors accordingly. They often see guidelines as an instrument to reduce cost and limit reimbursement to high risk conditions defined by arbitrary cutoffs. Therefore policy makers and all those responsible for the organization of the system should be involved in the development of a comprehensive preventive programme.

The Committee is well aware of the fact that issuing these guidelines on its own may not make the difference, but it can be helpful as part of a more comprehensive strategy of evidence based preventive medicine where it may serve as:

- A consensus among all partners involved in detection and control of arterial hypertension
- A basis for education and training
- A template for national joint task forces to adopt and/or adapt these guidelines in accord with national health policies and available resources
- A reference point based on scientific evidence to identify the most appropriate management tools for hypertension control
- A good basis for health economic purposes

IMPLEMENTATION TOOLS

Clinical Algorithm
Personal Digital Assistant (PDA) Downloads
Pocket Guide/Reference Cards

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

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European Society of Hypertension - Disease Specific Society

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Disclosure forms are available on the respective society Web Sites.

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Romanian Society of Cardiology - Medical Specialty Society
San Marino Society of Cardiology - Medical Specialty Society
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Turkish Society of Cardiology - Medical Specialty Society

GUIDELINE STATUS

This is the current release of the guideline.

This updates a previous guideline: 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2003 Jun;21(6):1011-53.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the European Society of Cardiology (ESC) Web site.

Print copies: Available from Oxford University Press, Great Clarendon Street, Oxford, OX2 6DP, UK, Tel: +44 (0) 1865 353263, Fax: +44 (0) 1865 353774, Web site: http://www.eurheartj.oxfordjournals.org/.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Management of arterial hypertension. Pocket guideline. Electronic copies: Available from the European Society of Cardiology (ESC) Web site. Also available for PDA download from the ESC Web site.
- Recommendations for guidelines production. A document for Task Force Members responsible for the production and updating of ESC guidelines. 2006 Jun 28. 21 p. Available from the ESC Web site.

Print copies: Available from Oxford University Press, Great Clarendon Street, Oxford, OX2 6DP, UK, Tel: +44 (0) 1865 353263, Fax: +44 (0) 1865 353774, Web site: http://www.eurheartj.org/.

PATIENT RESOURCES

None available

NGC STATUS

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